REMARKS

Claims 1, 2, and 5-10 were pending in the present application. By this Amendment, Applicants have amended claim 1 to recite "wherein the total amount of anti-free-radical agents present is up to 3.5% by weight." Claim 5 has been amended to remain consistent with this change. Claim 1 also has been amended to address the Examiner's concern under 35 U.S.C. §112, second paragraph. Support for the claim amendments can be found in the specification and claims as originally filed. Specifically, support for the amendment to the percentage range in claims 1 and 5 can be found, *inter alia*, at page 4, lines 8-10 of the specification. The present Amendment introduces no new matter, and thus, its entry is respectfully requested. Upon entry of the present Amendment, claims 1, 2, and 5-10 will be pending and under examination.

The October 20, 2004 Final Office Action

Claim Rejections under 35 U.S.C. §112, second paragraph

Claims 1, 2, and 5-10 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Specifically, the Examiner indicated that it is unclear whether claim 1 requires that one compound be selected from (a) or that the entire group (a) be selected. The Examiner identified the use of the word "and" in part (a) of the claim as a source of some confusion.

In response, Applicants assert that the claim is clear as written. Nevertheless, without conceding the correctness of the Examiner's position, but to expedite allowance of the subject application, Applicants have amended claim 1 by replacing "and" with "or" in part (a) so that

part (a) now recites "ascorbic acid, its salts, esters, glucosides or glucosamines." The claim as amended, refers, *inter alia*, to three anti-free-radical agents, each selected from a different one of groups (a)-(f) and thus it should be sufficiently clear to one of ordinary skill what subject matter is defined by the claims. Applicants believe that the above amendment to claim 1 fully overcomes the Examiner's concern and thus, respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. §103

Claims 1, 5, and 6 were rejected under 35 U.S.C. §103(a) as being unpatentable over Chen (U.S. Pat. No. 6,524,626) alone. Claims 2 and 7 were rejected as being unpatentable over Chen in view of Gubernick (U.S. Pat. No. 6,066,327) and claims 8-10 were rejected as being unpatentable over Chen and Gubernick, in view of Meybeck (U.S. Pat. No. 5,164,182). All of these references already have been made of record in the case. The Examiner has indicated that although the primary reference, Chen, discloses compositions with total antioxidant concentrations in excess of the amounts recited in the claims, lowering the concentrations to the claimed levels would have represented mere routine optimization of ranges and thus would have been obvious to one of ordinary skill in the art. The Examiner further asserted that Chen alone would have motivated one to reduce the amounts of ginseng to achieve "cost-efficiency." The Examiner also took the position that the claimed synergistic effect of the combined antioxidants simply reflects a natural flow that follows from Chen's suggested lowering of the concentrations.

In response, Applicants respectfully traverse the Examiner's rejection. Applicants first note that amended claim 1 now contains an even greater distinction between its total amount of antioxidant (a maximum of 3.5% w/w) and that of the Chen reference (which provides 28 specific Examples containing between 6 and 75.3% total antioxidant content).

Applicants respectfully disagree with several of the key positions the Examiner has taken in the Office Action, particularly with respect to the assertion that Chen provides a motivation to reduce the amount of antioxidants in the formulations. Applicants assert that there is nothing whatsoever in the Chen reference that would lead one of only ordinary skill to reduce the amount of ginseng (or other antioxidant) to the low levels recited in the Applicants' claims. Nor would there be any expectation that such levels would be effective, even if tried. To the contrary, Chen teaches, at columns 1-2 for example, that effectiveness depends on high concentrations (and a great variety of ingredients) and that Chen's skin formulations afford one the ability to receive such effective antioxidant levels while reducing the side effects that come with other forms of administration. As alluded to above, all of the many Examples provided in Chen use greater (and in some cases much greater) total concentrations of antioxidants than do the present claims. Furthermore, Applicants find the Examiner's reasoning with regard to the motivation provided by "cost efficiency" considerably flawed. The extraction method to which the Examiner referred (col. 3) appears merely to be designed to obtain as much ginseng from berries as possible. Applicants believe that the Examiner, however, has made an unreasonable leap and has improperly introduced an unsubstantiated opinion that the extraction process "would be costly."

The Examiner has then expanded this conclusion and assumed that because the process would be costly (in the Examiner's view), one of ordinary skill would be motivated to use as little ginseng as possible. Chen, however, gives no hint or suggestion that cost effectiveness is of any concern, that the process is in fact "costly," or that there is any feasible means to address the cost of extraction even if one were to think to do so. Chen simply does not provide any motivation to use low amounts of any component, despite the Examiner's statements. In fact, Chen only teaches the use of higher total antioxidant concentrations.

Furthermore, the Examiner has failed to recognize the ample evidence Applicants previously provided indicating that the synergistic effects of the claimed antioxidant combinations are indeed surprising, and therefore show the claimed combinations and concentration ranges to be both novel and unobvious. Applicants now have provided for the Examiner's consideration, the attached Declaration (under 37 C.F.R. 1.132) of Stewart Paul Long, a named inventor of the present application, which further supports the nonobviousness of the Applicants' claimed invention.

With respect to the applicability of the Chen reference, Applicants direct particular attention to paragraphs 8.1 and 8.2 of the Declaration. The purported advantages of Chen are realized through the topical application of a vitamin-rich fruit composition (col. 1, lines 24-27) to address the need for a skincare product which delivers natural vitamins, nutrients and other beneficial products to the skin without oral consumption and its resulting adverse side-effects (col. 2, lines 15-19). Chen has indicated that ginseng berry juice shows a high concentration of

essential vitamins (col, 2, lines 64-65) and that the juice from ginseng berries is useful in skincare products to deliver natural vitamins and nutrients to the skin (col. 2, lines 23-31). From column 3, line 60 on, Chen discloses that preferred embodiments of the invention combine ginseng berry juice with herbal ingredients and stimulants and/or other natural skin supplements to create an application that not only has a pleasing sensory effect on the user but also provides a great variety of ingredients essential to health and vitality. Thus, Chen in fact *teaches away* from reducing the quantity and number of ingredients to be combined with the ginseng berry juice.

Moreover, although the general description in Chen provides no disclosure of particular vitamins and nutrients that may be incorporated into ginseng berry formulations (other than ginseng root), the examples do provide guidance. For example, the Examples disclose the use, *inter alia*, of the following materials which may be classified as antioxidants in amounts in the ranges set forth below :

	Amount (%w/w)
Ginseng	3-68.3%
Grape seed extract	1-4%
Orange Peel	1-2%
Mulberry	1%
Kiwi	1%
Sage	1%
Grapefruit	1%
Vitamin C	1%
Tocopheryl acetate	1%

All of the 24 skincare examples contain 4 to 7 of the above-listed materials. The Chen disclosure does not teach the skilled person that there may be advantages in reducing the amount of anti-oxidant materials in the composition and does not suggest that a synergistic effect may be achieved with any combination of 3 anti-free-radical agents, much less the particular selection of anti-free radical agents recited in the Applicants' claims.

Paragraphs 8.1 and 8.2 of the Declaration note that Chen teaches that effective skincare compositions containing ginseng have a high concentration of antioxidants, confirmed by the presence of over 10% w/w antioxidant in 19 out of the 24 skincare Examples (additionally over 15% antioxidant is contained in 12 of these Examples). A further discussion of Example 22, highlighted as particularly relevant by the Examiner, is also included. This particular example contains 8% w/w antioxidant, more than twice the maximum 3.5% w/w total anti-oxidant of the present claims.

With respect to the criticality of the Applicants' claimed concentrations, the Declaration provides evidence of the synergistic effect achieved in accordance with the present invention. Both *in vitro* and *in vivo* results comparing the effectiveness of the individual antioxidants and when in combination are provided. Applicants note that, as stated in the Declaration, "[i]t is well known that the properties of anti-oxidants change when the amounts of anti-oxidants change; for example, they may change into pro-oxidants which cause oxidation, the effect we are trying to reduce" and that "[a]ny synergistic antioxidant effect found in the examples of Chen could not be predicted to be reproduced with lesser amounts of the same ingredients".

Applicants further point out that although Chen (col. 3, lines 8-9) discloses that ginseng and Vitamin C are anti-oxidants, there is no suggestion in Chen that the other materials listed above may be combined with ginseng for their anti-oxidant properties, in particular to give synergistic anti-oxidant properties.

In view of the above remarks and the attached Declaration, Applicants assert that Chen alone does not render obvious any of the Applicants' present claims.

Applicants assert that the secondary references cited by the Examiner do not cure the above deficiencies of the Chen reference. The Examiner has relied on Gubernick primarily for the teaching of substituting equivalent components into the Chen formulations (e.g., magnesium ascorbyl phosphate for ascorbic acid). The Examiner specifically asserted that Gubernick discloses an antioxidant mixture for a cosmetic composition which comprises magnesium ascorbyl phosphate and rosemary extract and thus has taken the position that it would have been obvious to modify the composition of Chen by substituting magnesium ascorbyl phosphate for ascorbic acid both because they are "equivalent" and because magnesium ascorbyl phosphate is the preferred form of Vitamin C. Applicants note, however, that in addition to the above arguments concerning the shortcomings of the Chen reference (which Gubernick does not overcome), Gubernick requires at least five antioxidants and does not suggest in any way that a combination of fewer than at least the specifically recited five could be effective. As Applicants have shown, the claimed synergistic effect, and therefore the ability to use fewer antioxidants in lesser amounts, is a surprising and unexpected result over the teachings in the art.

The Examiner has again relied on Meybeck for its teaching of low concentrations of mulberry extract. Meybeck, however, does not cure the above deficiencies of the Chen and Gubernick references and thus does not render the claims obvious when combined with those references. As Applicants have previously argued, Meybeck's teachings regarding the activity of mulberry extract appear only in the context of its particular use as incorporated into a lamellar phase or liposome. One would not have been motivated to combine these teachings with those of the prior art references because doing so would seem to offer no benefit. Accordingly, for at least the reasons set forth above, no combination of the references cited by the Examiner renders obvious the Applicants' present claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 2, and 5-10 under 35 U.S.C. §103.

Examiner's rejection based on Double Patenting

In the October 20, 2004 Final Office Action, the Examiner repeated the previously set forth provisional rejection of the claims under the judicially created doctrine of obviousness-type double patenting, (as being obvious over claims 1-13 of copending Application No. 10/030147).

In response, Applicants point out that an appropriate Terminal Disclaimer was filed October 7, 2004, which fully obviates this rejection. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the provisional double-patenting rejection.

In view of the above remarks, amendments, and attached Declaration, Applicants believe that the Examiner's rejections set forth in the October 20, 2004 Final Office Action have been fully overcome and that the present application is in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

No fee is believed due in connection with the filing of this Amendment. If, however, any fee is deemed necessary, authorization is hereby given to charge such fee, or credit any overpayment to Deposit Account No. 02-2135.

Respectfully submitted,

Date: December 20, 2004

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Attachment: Declaration of Stewart Paul Long

2955-194.am3.wpd

IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

Serial No :	10/069,975	) Examiner:
		) Gina C. Yu
Inventors :	Melanie Ann PYKETTet al	)
		)
Filed :	OCTOBER 10, 2002	)

For : SKIN CARE COMPOSITION AGAINST FREE RADICALS

DECLARATION OF STEWART PAUL LONG

I, STEWART PAUL LONG, of 22 Hilltop Drive, Oakham, Rutland, LE15 6NF, United Kingdom, declare as follows:

My Background and Experience

1. I hold a Master of Science (M.Sc.) degree in Biochemistry from the University of Liverpool.

2. After graduation from university, I worked for approximately eight years for Unilever PLC, conducting research on skincare and haircare products. In 1998 I joined The Boots Company PLC where I now hold the position of Scientific Adviser (Biotechnology and Haircare). During my time I have managed the Product Evaluation Group, with responsibility for ensuring the safety and efficacy of all products and currently manage the Claims Development team, responsible for developing novel test methodologies to investigate product safety and performance

3. In my work at Boots I have gained extensive experience of the development of research methodologies concerned with skincare products, and

in the use of anti-oxidants in such products. I am one of the inventors of the present application.

Introduction

4. As we age, our skin undergoes changes such as becoming thinner, more easily damaged and less elastic. Skincare formulations contain a number of efficacious ingredients to reduce the effects of ageing. Such compositions must also be cosmetically acceptable to the consumer and have a good shelf life.

5. The primary cause of skin ageing and skin cancer is solar radiation. The action of UV generates free radicals in the skin, which damage DNA, protein and cell membranes. As a result, discolouration, wrinkling, skin sagging, loss of elasticity, mottling and precancers can occur. Oxygen radicals and other free radicals are key factors in damage to the skin. It is known that many small molecules, including oxygen, may be activated by factors such as radiation , chemicals and drugs to yield reactive oxygen species (ROS) and free radicals, which can initiate chain reaction. Many different consequences of such a chain reaction contribute to ageing and susceptibility to cancer. Firstly, the cross linkage of collagen causes thin inflexible wrinkled skin. Secondly, the breakdown of hyaluronic acid diminishes the water holding capacity. Thirdly, free radicals attack phospholipids in the cell membrane thereby getting access to DNA and enhancing the risk of skin cancer. Direct damage to the DNA by radicals is also a possibility.

6. In skincare compositions, in order to reduce the accelerated ageing effect of the sun on the skin, it is known to include ingredients that contain sunscreen agents that either reflect or absorb solar rays. It is also known to use antioxidants that react with the free radicals and so terminate the chain of reactions that free radicals customarily propagate which so damage the skin. Furthermore, the use of vitamins and herbal extracts is known, although customarily high levels of the materials need to be used to achieve appropriate

efficacy and this can lead to products which are less cosmetically acceptable to the customer.

7. According to our present invention, we have found that if three anti-oxidants are combined out of six particular classes of materials, namely

(a) ascorbic acid, its salts, esters, glucosides or glucosamines;
(b) morus alba;
(c) origanum vulgare;
(d) panax ginseng;
(e) rosmarinus officinalis; and
(f) grape seed oil;

we achieve a synergistic effect which allows small concentrations (ie 3.5% w/w or less) of antioxidants to be used in skincare formulations. Thus, we have provided a synergistic improvement in activity to allow significant protection against accelerated skin ageing without the drawback of aesthetically unpleasant product appearance.

8.1 I have read the specification of US Patent No. 6524626 (Chen et al) relating to skincare compositions comprising ginseng berry extract in combination with other skin nutrients. Chen discloses that an analysis of the juice from ginseng berries has shown it to contain a high concentration of essential vitamins, including riboflavin, vitamin A, vitamin E and beta Carotene. It also discloses that ginseng berry juice acts as an antioxidant. Furthermore, Chen discloses that the juice from ginseng berries may be combined with herbal supplements and stimulants and/or other natural skin supplements. There are twenty four illustrative Examples of skincare formulations which contain many different combinations of ginseng with different natural products. A number of these additional natural products have anti-oxidant activity, for example, Grape Seed extract, Orange Peel, *Hibiscus Sabdariff,* Mulberry Leaf, Tocopheryl Acetate, Sage, Grapefruit, Kiwi and Ascorbic acid. Chen teaches that a significant number of these natural products are required for the skincare

formulation to be effective. All the skincare example formulations are disclosed as having a mixture of at least four materials that are antioxidants, with most examples containing at least six materials that are antioxidants. Chen also teaches that high levels of anti-oxidants are needed in skincare compositions. Most of the skincare examples have a total anti-oxidant concentration above 10% w/w, with two containing greater than 70% w/w of anti-oxidant materials. It is well known that the properties of anti-oxidants change when the amounts of anti-oxidants change; for example, they may change into pro-oxidants which cause oxidation, the effect we are trying to reduce. In my opinion it would not obvious to a person skilled in the art that reducing the number and amounts of antioxidants from the levels described in Chen would lead to skincare formulations with effective antioxidant properties.

8.2 Furthermore, Chen does not suggest that the level of antioxidants used in a skincare formulation could be lowered below the minimum level of 6% found in Example 23 (Ginseng Berry Extract 3%, Grape Seed Extract 1%, Kiwi 1% and Tocopheryl Acetate 1%) for a body wash detergent product that is washed off soon after application. Examples of formulations to be applied and left on the skin to provide the desired anti-oxidant effect contain more than this minimum amount of total anti-oxidant. Example 22 contains the minimum antioxidant level of such leave-on examples, with a total of 8% w/w antioxidant (Ginseng Berry Extract 2%, Ginseng Root Extract 2%, Grape Seed Extract 2%, Tocopheryl Acetate 1% and Vitamin C 1%). This example does contain a mixture of some of the antioxidant materials that we have found to be particularly effective, but at a total antioxidant level of between two and three times our maximum amount claimed. Any synergistic anti-oxidant effect found in the Examples of Chen could not be predicted to be reproduced with lesser amounts of the same ingredients. In my opinion, this disclosure would give the person skilled in the art no reason to reduce the workable quantities of the antioxidants used in these two particular examples in the expectation that a similar antioxidant effect would be obtained.

This disclosure provides no motivation to use a combination of three antioxidants at a total antioxidant concentration of 3.5% w/w or less.

9. The following experiments were carried out in our laboratories to investigate the effects of combinations of antioxidants, with a view to developing improved skincare products.

Methodologies

10. *In vitro* Tests

A 1% lipid stock solution was prepared by dissolving linoleic acid in an aqueous solution of octoxynol-9 (Triton X-100). Stock solutions in aqueous TBS buffer of the ascorbic acid (and derivatives) antioxidants were prepared at 15% and plant derived extract antioxidants at 1.0%. In experiments where the antioxidants were tested individually, 25µl of the lipid stock was vortexed in an ependorf together with 5µl of the antioxidant solution and 20µl of Triton X~100 (mixture of water and detergent used to dissolve the lipid). In experiments where the antioxidants were tested in combination, 25µl of the lipid stock is vortexed in an ependorf together with 5µl of each of the antioxidant solutions and 10µl of Triton X100. The final concentration of the lipid was 0.5% and of the ascorbic acid (and derivatives) antioxidants was 1.5% and of the plant derived extract antioxidants 0.1% and 0.1% respectively.

The control sample used in the experiment was a combination of 25µl of the lipid stock solution and 25µl of TritonX100 and water. This solution contained no antioxidants. Samples of this control were taken before irradiation to act as untreated controls.

Using a micropipette plate 7.5µl of each sample was pipetted into 3 wells, i.e. in triplicate, and irradiated with UV light for 40 minutes. After irradiation an assay called the lipid peroxidation assay was carried out. This determined the

amount of peroxides in each well. The reaction that occurs causes a colour change from colourless to blue which is measured colourimetrically at 675nm. The more peroxides present the darker the blue colouration and the higher the observed absorbance.

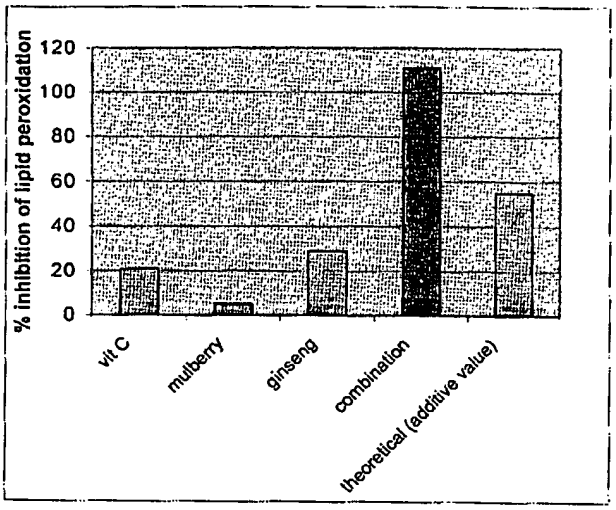
11. *In vivo* Tests

Test formulations containing 1% w/w total antioxidants and control formulations containing no antioxidants were applied to the skin of the forearm of volunteers. One hour later an adhesive disc was applied to the skin to sample skin cells and the disc was then irradiated with broad spectrum UVA/B to induce oxidation of the lipid. Following extraction of the lipid into methanol, the degree of lipid hydroperoxides (free radical generated damage) formed were measured colourimetrically. The degree of protection afforded by the antioxidants is thus measured and compared to unirradiated and irradiated controls.

Results

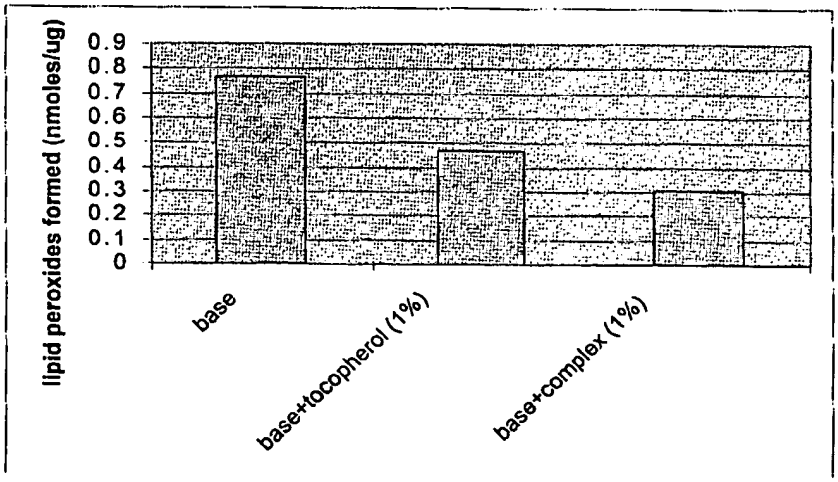
12. *In vivo* Measurements

12.1 A comparison was made between the effects of each of sodium ascorbyl phosphate, mulberry (morus alba) and panax ginseng alone and the combination of all three antioxidants in amounts of 0.5%, 0.25% and 0.25% w/w respectively. The results are shown in the graph below:



The graph shows that when used singly in the formulation, the antioxidants provide limited protection against lipid peroxidation. When combined, there is a synergistic, protective effect. The theoretical additive effect is also shown for comparison. This is the predicted protection that should be expected by combining the single antioxidants. It can be seen that it is considerably less than the experimental result, confirming the synergistic effect.

12.2 A comparison was made between the effects of each of a base moisturiser formulation (without anti-oxidant), the same base formulation with 1% tocopherol (a widely used antioxidant) and the same base formulation with 1% antioxidant complex (sodium ascorbyl phosphate 0.5%, mulberry (morus alba) 0.25% and panax ginseng 0.25%). The results are shown in the graph below:

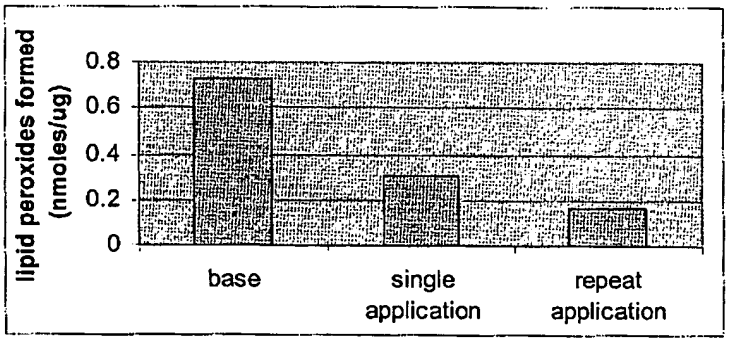


The graph shows that the formulation containing 1% tocopherol provides protection against lipid peroxidation, compared to the base formulation. However, it can be seen that the antioxidant complex is significantly more effective than tocopherol ($p < 0.01$). This demonstrates the greater protection afforded by the novel antioxidant complex.

12.3 A comparison was made between the effects of the base moisturiser formulation and the same formulation with 1% by weight antioxidant complex added.

The graph shows that a clear and statistically significant ($p<0.001$) protection against damage is provided by the addition of the antioxidant complex, compared to the standard moisturiser base.

In addition, applying the formulation containing antioxidants to the skin for 4 consecutive days before exposing to solar simulated light on the fifth day (no product was applied on the day of exposure) provides greater protection than that obtained from a single application. This demonstrates that the antioxidants are



delivered to the skin and reinforce the natural skin defences.

12.4 10 female volunteers used the day cream formulation for 2 weeks on one half of the face. Skin strippings were taken from both sides of the face at the start of the study and after two weeks (no product applied on day of stripping).

The skin samples were UV irradiated and the levels of lipid peroxides formed were measured. It was found that after two weeks use of the product containing the antioxidant complex, a significant reduction in lipid peroxidation was measured following a UV challenge, compared to the untreated samples ($p<0.01$). The level of UV damage was almost halved by use of the protective antioxidant complex containing formulation. This demonstrates that regular use of the formulation delivers antioxidants into the skin and that they are able to provide protection against free radical damage- one of the major causes of premature skin ageing.

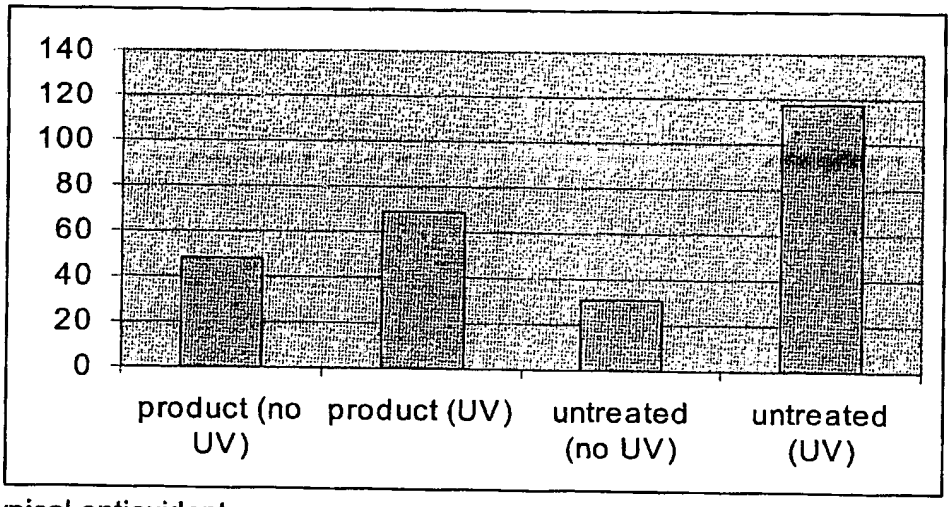
12.5 In addition to the measurements of free radical protection described above, a larger volunteer group of women (from whom the 10 panellists above were randomly selected for biochemical analysis), comprising 40 volunteers, used the test formulation for a total period of twelve weeks. A skincare product containing 1% by weight antioxidant complex (ascorbyl phosphate, morus alba and panax ginseng) was applied daily throughout the study. After 12 weeks (and throughout the study) expert visible assessment of skin condition changes were performed, using a panel of trained assessors. In addition, silicon replicas of the skin were taken and profilometry was used to measure changes in skin wrinkling and fine lines. The volunteers also undertook self assessment of their skin condition, scoring the changes on scientifically designed questionnaires.

After 12 weeks of product use, it was found that statistically significant changes could be seen in key signs of premature skin ageing:

- the depth of fine lines and wrinkles was measurably decreased
- skin texture was noticeably improved
- skin appeared fresher, healthier and more radiant.

From these studies we conclude that the product containing 1% by weight antioxidant complex (ascorbyl phosphate, morus alba and panax ginseng) provides significant protection against free radical damage and that regular use

will help reduce the signs of premature ageing. The novel antioxidant complex is therefore a highly effective technology which offers advantages compared to



typical antioxidants.

13. *In vitro* measurements

13.1 This tests the ability of antioxidants to protect lipids from the damaging effects of UV light. In the test the antioxidant or combination of antioxidants is mixed with a known skin lipid (linoleic acid) and irradiated using UV light. The results are expressed as the % inhibition of free radical mediated lipid peroxidation compared to that achieved using the vehicle alone. The values are given below for individual anti-oxidants. A value of 0% indicates no effect in protecting lipids from UV radiation. A value of 100% indicates complete protection of the lipids following UV irradiation.

Anti-oxidant	% inhibition
Morus alba (m)	0

Origanum vulgarum (or)	49
Panax ginseng (gin)	5.7
Sodium ascorbyl phosphate (nap)	21
Grape seed (gs)	0
Observed effect of nap/gin/or	100
Predicted effect of nap/gin/or	75.7
Observed effect of nap/m/or	100
Predicted effect of nap/m/or	70
Observed effect of nap/m/gs	81
Predicted effect of nap/m/gs	21

Thus it can be seen that the observed inhibiting effect of using the above combinations of anti-oxidants is greater than that which would be expected from the sum of the contributions of the individual antioxidants.

13.2 In a second series of experiments using antioxidants collected in a later season, the following results were obtained:

Anti-oxidant	% inhibition
Morus alba (m)	37
Origanum vulgarum (or)	29
Rosmarinus officinalis (r)	15
Panax ginseng (gin)	10
Observed effect of r/gin/or	88
Predicted effect of r/gin/or	54
Observed effect of gin/m/or	93
Predicted effect of gin/m/or	76

Again, it can be seen that the observed inhibiting effect of using the above combinations of anti-oxidants is greater than that which would be expected from the sum of the contributions of the individual antioxidants.

13.3 In a further series of measurements, the following series of results were obtained for individual anti-oxidants, expressed as the % inhibition of free radical mediated lipid peroxidation compared to that achieved using the vehicle alone.

Antioxidant	% inhibition
Morus alba (m)	0
Origanum vulgare (or)	29
Rosmarinus officinalis (r)	15
Panax ginseng (gin)	5.7
Grape seed (gs)	0
Ascorbyl phosphate (ap)	49
Ascorbic acid ester (aae)	48

The results obtained for combinations of three antioxidants (at the same total antioxidant concentration as for the individual antioxidants) are shown, in comparison with the individual components, in Figures 1, 2 and 3. These show synergistic effects for the following combinations of anti-oxidants:

(Figure 1) Rosmarinus officinalis / Panax ginseng / Ascorbyl phosphate
Panax ginseng / Morus alba / Ascorbyl phosphate
Rosmarinus officinalis / Morus alba / Ascorbyl phosphate

(Figure 2) Rosmarinus officinalis / Oreganum vulgarum / Grape seed
Morus alba / Oreganum vulgarum / Panax ginseng
Grape seed / Oreganum vulgarum / Panax ginseng
Rosmarinus officinalis / Oreganum vulgarum / Panax ginseng

(Figure 3) Ascorbyl phosphate / Oreganum vulgarum / Morus alba

Panax ginseng / Oreganum vulgarum / Ascorbyl phosphate
Oreganum vulgarum / Ascorbic acid ester / Panax ginseng
Ascorbyl phosphate / Oreganum vulgarum / Rosmarinus officinalis
Ascorbic acid ester / Oreganum vulgarum / Morus alba
Grape seed / Ascorbyl phosphate / Morus alba
Ascorbic acid ester / Grape seed / Rosmarinus officinalis

13.4 Further measurements were made, in a separate series of experiments, and the following results, expressed as the % inhibition of free radical mediated lipid peroxidation, were obtained:

Combination	Predicted % inhibition	Actual % inhibition
ap/m/or	78	100
ap/m/gin	54.7	98.6
ap/m/gs	49	81
ap/gin/r	69.7	92
ap/m/r	64	99.9
or/m/gin	34.7	93
or/gin/gs	34.7	100
r/or/gin	49.7	88
ap/or/gin	69.7	100
or/aae/gin	48	88
aae/gs/r	63	94

The results above show a synergistic effect for the above combinations of 3 antioxidants.

Conclusions

14. The results show that lipid peroxidation can be inhibited by specific combinations of antioxidants.

15. Surprisingly, the results show that combinations of three antioxidants selected from:

(a) ascorbic acid, its salts, esters, glucosides or glucosamines;
(b) morus alba;
(c) origanum vulgare;
(d) panax ginseng;
(e) rosmarinus officinalis; and
(f) grape seed extract;
wherein the total amount of anti-free-radicals is up to 3.5% by weight,

are synergistic in that the effect of such combinations is greater than would be predicted on the basis of the effects of the individual antioxidants alone. This has been demonstrated for all of the following combinations of antioxidants:

Rosmarinus officinalis / Panax ginseng / Ascorbyl Phosphate
Panax ginseng / Morus alba / Ascorbyl phosphate
Rosmarinus officinalis / Morus alba / Ascorbyl phosphate
Morus alba / Origanum vulgare / Panax ginseng
Grapeseed / Origanum vulgare / Panax ginseng
Rosmarinus officinalis / Origanum vulgare / Panax ginseng
Ascorbyl Phosphate / Origanum vulgare / Morus alba
Panax ginseng / Origanum vulgare / Ascorbyl Phosphate
Origanum vulgare / Ascorbic acid ester / Panax ginseng
Ascorbyl phosphate / Morus alba / Grape seed
Ascorbic acid ester / Grape seed / Rosmarinus officinalis
Rosmarinus officinalis / Origanum vulgare / Grape seed
Ascorbyl phosphate / Origanum vulgare / Rosmarinus officinalis
Ascorbic acid ester / Origanum vulgare / Morus alba

16. In view of the fact that a synergistic effect has been demonstrated for a substantial proportion of all possible combinations of antioxidants covered by the claims of the present application, and in view of the fact that all of the anti-oxidants listed in the claims of the application occur in at least one of the combinations for which synergy has been demonstrated, I believe it is reasonable

to suppose that other combinations falling within the scope of the claims would exhibit similar properties.

17. I do not believe that the synergistic effects described herein could have been predicted from the properties of the individual antioxidants or from the prior art.

Figure 1

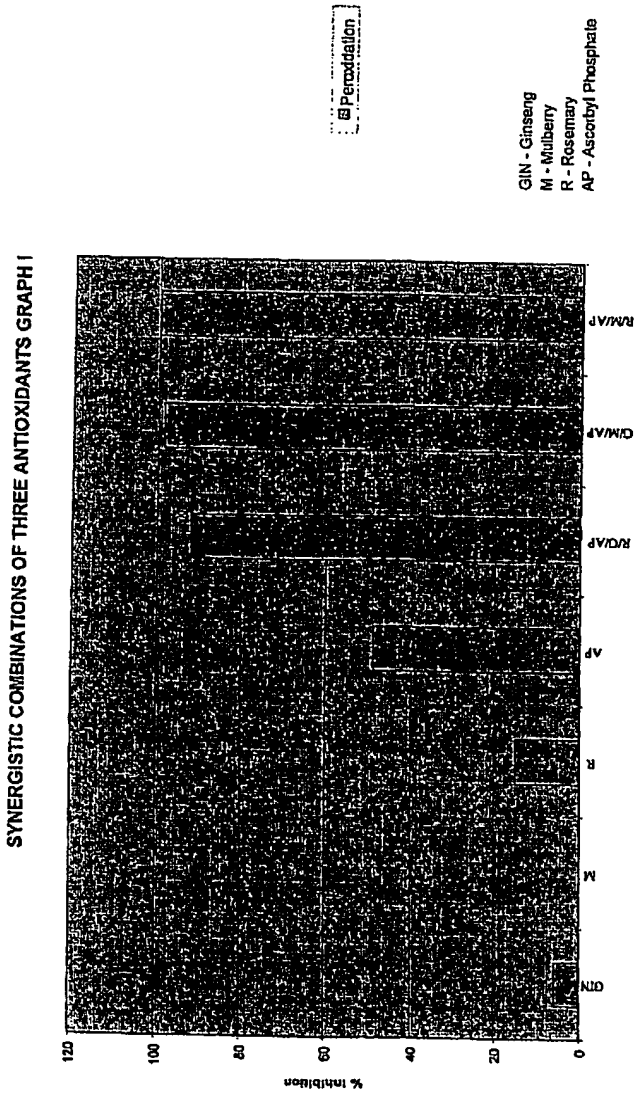

SYNERGISTIC COMBINATIONS OF THREE ANTIOXIDANTS GRAPH I
Peroxidation
GIN - Ginseng
M - Mulberry
R - Rosemary
AP - Ascorbyl Phosphate
% Inhibition
120
100
80
60
40
20
0
GIN
M
R
AP
R/G/AP
G/M/AP
R/M/AP

Figure 2

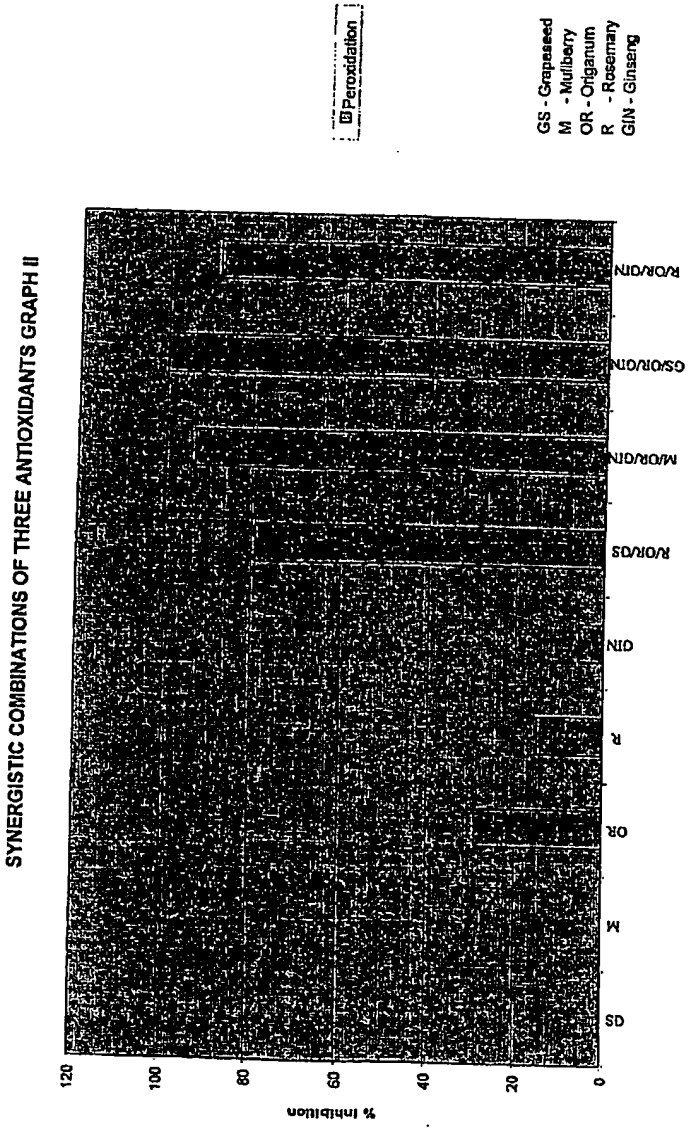
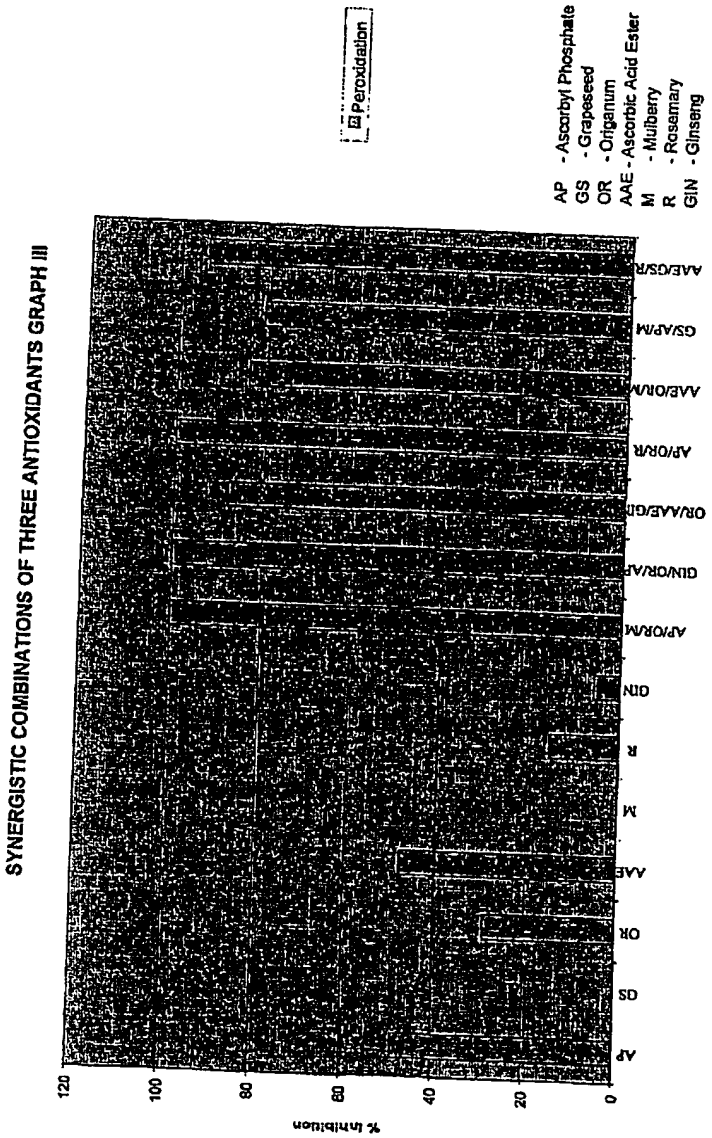

SYNERGISTIC COMBINATIONS OF THREE ANTIOXIDANTS GRAPH II
Peroxidation
GS - Grapeseed
M - Mulberry
OR - Origanum
R - Rosemary
GIN - Ginseng
R/OR/GIN
GS/OR/GIN
M/OR/GIN
R/OR/GS
GIN
R
OR
M
GS
120
100
80
60
40
20
0
% inhibition

Figure 3


SYNERGISTIC COMBINATIONS OF THREE ANTIOXIDANTS GRAPH III
Peroxidation
AP - Ascorbyl Phosphate
GS - Grapeseed
OR - Origanum
AAE - Ascorbic Acid Ester
M - Mulberry
R - Rosemary
GIN - Ginseng
% Inhibition
120
100
80
60
40
20
0
AP
GS
OR
AAE
M
R
GIN
AP/OR/M
GIN/OR/AP
OR/AAE/GI
AP/OR/R
AAE/OR/M
GS/AP/M
AAE/GS/R

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed : _____

Stewart Paul LONG

Date : 16/12/04